REMARKS

Claims 1-30 are pending. Claims 9-11, 29, and 30 stand withdrawn from consideration as being drawn to nonelected subject matter. Applicants have added new claims 31-50. Claims 1-8, 12-28, and 31-50 will therefore be pending upon entry of the proposed amendments.

Applicants wish to thank Examiner Winston for participating in the March 7, 2007 telephone interview.

Applicants have inserted the phrase " wherein the reconstitution solution of mixed solvents comprises water for injection and a co-solvent" at the end of claim 1. Support for this amendment can be found throughout the Specification, e.g., at page 4, third full paragraph and page 5, fourth paragraph. Applicants have amended claims 5, 6, and 8, each of which depend from claim 1, to comport in scope with claim 1 as currently amended. Support for the amendment to claim 26 can be found throughout the Specification, e.g., at page 4, third full paragraph; and page 5, fourth paragraph.

Applicants have replaced "water" in claim 12 with "water for injection." Support for this amendment can be found throughout the Specification, e.g., at page 4, third full paragraph. Support for the amendments to claims 20-25 can be found throughout the Specification, e.g., at page 4, second and third full paragraphs.

Support for new claims 31-50 can be found throughout the Specification, e.g., at page 2, second full paragraph; page 4, third full paragraph; and page 5, fourth paragraph.

No new matter is introduced by these amendments.

Brief Summary of Claimed Subject Matter

The present claims are directed to kits and pharmaceutical compositions for the parenteral administration of didemnin compounds (e.g., aplidine, which is also known as dehydrodidemnin B).

Independent claim 1 as currently amended is directed to kits that include "firstly a lyophilized didemnin preparation comprising water-soluble material and secondly, and separately contained, a reconstitution solution of mixed solvents, wherein the reconstitution solution of mixed solvents comprises water for injection and a co-solvent" (emphasis added). The kits provide a stable dosage form that can be reconstituted for administration by injection.

New claim 31, which depends from claim 1, requires:

(i) the water for injection is present in an amount sufficient to allow solubilization of the water soluble material, and

(ii) the co-solvent is present in an amount sufficient to allow solubilization of the didemnin in the lyophilized didemnin preparation.

Independent claim 12 as currently amended is directed to reconstituted pharmaceutical compositions that include: "a didemnin compound; a water soluble material; a surfactant; an alkanol; and water for injection" (emphasis added).

New claim 32, which depends from claim 1, requires:

(i) the water for injection is present in an amount sufficient to allow solubilization of the water soluble material, and

(ii) the alkanol is present in an amount sufficient to allow solubilization of the didemnin compound.

New independent claim 33 is directed to kits that include "firstly a lyophilized didemnin preparation comprising water-soluble material and secondly, and separately contained, a reconstitution solution of mixed solvents, wherein the reconstitution solution of mixed solvents comprises water and a co-solvent, wherein:

(i) the water is present in an amount sufficient to allow solubilization of the water soluble material, and

(ii) the co-solvent is present in an amount sufficient to allow solubilization of the didemnin in the lyophilized didemnin preparation."

New independent claim 41 is directed to reconstituted pharmaceutical compositions that include:

"a didemnin compound;

a water soluble material;

a surfactant;

an alkanol, wherein the alkanol is present in an amount sufficient to allow solubilization of the didemnin compound; and

water, wherein the water is present in an amount sufficient to allow solubilization of the water soluble material."

The claimed kits and pharmaceutical compositions address some of the problems associated with prior efforts to obtain stable, soluble pharmaceutical preparations that are suitable for the parenteral (e.g., intravenous) administration of didemnins. Stable didemnin pharmaceutical preparations can typically be achieved by the inclusion of a bulking agent as part of the preparation. A preferred bulking agent for this purpose is mannitol, which is water soluble. The didemnins (e.g., aplidine), however, tend to have only rather limited water solubility. This difference in water solubility can be problematic for parenteral administration of didemnins, such as aplidine, because water-based vehicles are typically the liquid vehicles of choice for parenteral routes of administration. The inventors, in addressing the aforementioned

problems, have discovered lyophilized didemnin preparations, which are both stable and permit solubilization of a didemnin (e.g., aplidine) and a water soluble adjuvant(s) (e.g., mannitol) in water based vehicles that are suitable for parenteral administration to a cancer patient.

Rejection under 35 U.S.C. § 103

Claims 1-8 and 12-28 are rejected as being unpatentable over Crumb et al., U.S. Patent 6,030,943 (Crumb) in view of Gyory et al., U.S. Patent 5,883,135 (Gyory).

Applicants respectfully disagree with the grounds for rejection, however, to expedite prosecution, Applicants have amended independent claim 1 to require that the reconstitution solution comprises "water for injection and a co-solvent" and claim 12 to require the presence of "water for injection" instead of "water." Applicants submit that claims 1-8 and 12-28 (as well as new claims 31-50) are patentable over Crumb and Gyory (alone or in combination) for at least the reasons given below.

Crumb discloses that aplidine can be used as an L-type calcium channel enhancer (Crumb, col. 2, lines 33-34). Crumb teaches that aplidine can be administered "intravenously or by injection" using "liquids" that contain a single solvent, namely water (see Crumb at col. 6, lines 12-18). A co-solvent (e.g., an alkanol) is never mentioned in Crumb.

Gyory is concerned exclusively with transdermal delivery of drugs (not a didemnin, didemnins are not mentioned in Gyory), stating: "this invention arose from a desire to improve on prior art technology in the field of transdermal electrotransport delivery" (Gyory at col. 3, lines 34-36). More specifically, Gyory discloses compositions for transdermal delivery that include a drug, a short chain alcohol, a long chain alcohol, and water. Gyory reports that the compositions reduce "electrical resistance of body surfaces, such as the skin, mucosa, and nails," thereby enhancing the "transdermal electrotransport drug flux" (Gyory at col. 3, lines 49-51 and col. 4, lines 60-64). Thus, Gyory teaches the use of a co-solvent (i.e., a combination of a short and long chain alcohol) only for enhancing transmission of a drug through the skin.

The Office argues that it would have been obvious to combine Crumb and Gyory to arrive at the claimed kits and compositions. In particular, the Office argues on page 4 of the Office Action:

> Furthermore, Gyory et al. beneficially teach (see, e.g. column 3 line 5-10 and also in other publication page 1 see Ferber et. al.) that the claimed active ingredient of alkanol is an effective carrier and/or effective delivery enhancer to aid in the administration of an active ingredient to a subject.

Applicants respectfully disagree.

The claims as presently amended are limited to kits and compositions having water for injection (as referred to as "WFI") and a co-solvent; or kits and compositions having water present in an amount sufficient to allow solubilization of a water soluble material and a co-solvent (e.g., an alkanol) present in an amount sufficient to allow solubilization of a didemnin. In contrast, all Gyory teaches is that the addition of a co-solvent enhances the transmission of a drug through the skin. As such, Applicants submit that even if one could properly combine Crumb and Gyory, the present claims would still be patentable over Crumb and Gyory (alone or in combination). This is discussed in more detail below.

The claims that are limited to kits and compositions having water for injection (a specific grade of water suitable for intravenous administration) and a co-solvent are patentable because while the cited combination of references may suggest (at best) making a transdermal preparation, it does not fairly suggest using a grade of water, namely water for injection, which is suitable for intravenous administration. Again, Applicants stress that the term "water for injection" is not an intended use. Rather, the term "water for injection" refers to a specific grade of water. See, e.g., the attached excerpt from *The Merck Index*, which states, in part (bold emphasis in original, underline emphasis added):

> **Pyrogen-free water** (water for injection) is distilled water rendered free of fever-producing proteins (bacteria and their metabolic products). Method of prepn: Ishizuka *et al., C.A.* 49, 15177.

The claims that are limited to kits and compositions having water present in an amount sufficient to allow solubilization of a water soluble material and a co-solvent (e.g., an alkanol) present in an amount sufficient to allow solubilization of a didemnin are not taught or suggested by the prior art of record. The co-solvent in Gyory (i.e., a combination of a short and long chain alcohol) is never mentioned for solubilization, but rather for enhancing transdermal electrotransport drug flux. Gyory actually appears to be quite unconcerned with the drug solubilization issues facing the present inventors. In fact, Gyory specifically indicates that the drug being delivered is loaded into the transdermal delivery devices as "[a]n aqueous solution" (Gyory at col.8, line 27, emphasis added).

Finally, to argue that one should select aplidine from Crumb; select water for injection from somewhere in the art; and select a co-solvent from Gyory (while at the same time ignoring Gyory's instructions to make a transdermal preparation) amounts to nothing more than using the claimed invention as a blueprint to identify and piece together its component parts in the prior art. However, such a hindsight-based obviousness analysis cannot be used to defeat patentability. *See, e.g., In re Fine* 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988):

> But this court has said, "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." *W.L. Gore,* 721 F.2d at 1553, 220 USPQ at 312-13. It is essential that "the decisionmaker forget what he or she has been taught at trial about the claimed invention and cast the mind back to the time the invention was made ... to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art." *Id.* One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.

In view of the foregoing, Applicants respectfully request that the rejection be reconsidered and withdrawn and not be applied to new claims 31-50.

Applicants submit that all claims are in condition for allowance.

Enclosed is a $1,020 check for the Three Mont Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 14620-012US1.

Respectfully submitted,

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